

REMARKS

Upon entry of this amendment, claims 1-62 are pending. Claims 18, 32, 34, 36, 37, 41-49, 56, 57, 61, and 62 have been withdrawn. Claims 1-7, 11, 12, 40, 55, and 58 have been amended. Applicant respectfully submits that the amendments do not introduce new matter and that they are made without any intention to abandon the subject matter as filed, but with the intention that claims of the same, greater, or lesser scope may be filed in a continuing application.

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 4-6, 8, 9, 11, 19-21, 24, 28, 29-31, 33, 35, 38, 50-55, 58, and 59 under 35 U.S.C. §102(b), contending that the claims are anticipated by Yap *et al.* (1999) J. Am. Soc. Nephrol. 10:529-537 ("Yap *et al.*"). Applicant traverses the rejection to the extent it is maintained over the claims as amended.

Anticipation under 35 U.S.C. §102 requires that all of the elements and limitations of the claims at issue be found within a single prior art reference. *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Applicant submits that Yap *et al.* does not disclose all of the elements and limitations of Applicant's claims. Yap *et al.* discloses alterations in interleukin 2, interferon γ , interleukin 4, and interleukin 13 mRNA levels in CD4+ and CD8+ T cells from steroid-responsive children with idiopathic nephrotic syndrome in relapse or remission, as well as normal and viral infection control subjects. Cytokine mRNA levels were compared to RNA levels for a housekeeping gene, cyclophilin. Applicant submits that Yap *et al.* does not disclose at least one step in the rejected independent claims as amended. For example, Yap *et al.* does not determine steroid responsiveness in their subjects (as recited in claim 1), does not determine an effective dose of a steroid (as recited in claim 4), does not monitor their subjects' ability to respond to a steroid (as recited in claim 5), and does not determine drug responsiveness in their subjects (as recited in claim 6). This is because the steroid responsiveness of the subjects of the Yap *et al.* study is already known (with regard to claims 1, 4, and 5) or because drug responsiveness is not at issue (with regard to claim 6) in the Yap *et al.* study and therefore need not be determined or

monitored. Therefore, Applicant submits that Yap *et al.* does not disclose each and every element of the invention claimed in Applicant's amended claims 1, 4, 5, and 6. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 4, 5, and 6 and the claims depending therefrom.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 2, 3, 7, 10, 12-17, 22, 23, 25, 26, and 27 under 35 U.S.C. §103(a), contending that the claims are unpatentable over Yap *et al.*, further in view of Steel *et al.* (1996) Scand. J. Immunol. 44:493-500 ("Steel *et al.*"). Applicant traverses the rejection to the extent it is maintained over the claims as amended.

The proper standard for evaluating obviousness requires a determination of (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicant's disclosure. *See id. citing In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Finally, section 103 requires that the suggestion or incentive to combine prior art references must be derived from the teachings of the references. *See ACS Hosp. Systems, Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577, 21 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

Applicant submits that there is no motivation in either Yap *et al.* or Steel *et al.* to combine their disclosures to make Applicant's claimed invention. Yap *et al.* does not disclose determining steroid responsiveness in a tissue, body fluid, or cell (as recited in claim 1), does not disclose determining steroid responsiveness of a subject based upon the comparison of pre-treatment RNA levels between a first and second gene (first normalized value) to post-treatment RNA levels of the first and second gene (second normalized value) (as recited in claim 3), and does not disclose determining drug responsiveness of a tissue, body fluid or cell (as recited in claim 7). Yap *et al.* provides no motivation to examine steroid responsiveness in their subjects or in cells derived from their subjects because the steroid responsiveness of each of the subjects of the Yap *et al.* study was already known. "The patients were stratified into those who were

steroid-dependent, and therefore on steroid treatment, and those who were not on steroids during the time of blood sample.” Yap *et al.* at page 531, column 2, line 34 to page 532, column 1, line 1. Although some of the steroid responsive subjects were receiving steroids, their responsiveness was not being determined or monitored. Thus, Yap *et al.* could not provide a motivation to examine steroid responsiveness in their subjects or cells derived from their subjects.

Likewise, Applicant submits that Yap *et al.* provides no motivation to examine drug responsiveness in their subjects or in cells derived from their subjects because Yap *et al.* are not studying drug responsiveness. On the contrary, Yap *et al.* states that none of the children were on angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs, and none were previously given cyclosporin or cyclophosphamide, because these drugs might have affected the interpretation of the cytokine gene expression. Yap *et al.* at page 530, column 1, lines 30-36. Thus, Yap *et al.* teach away from Applicant’s claimed invention, which is directed at the determination or monitoring of steroid or drug responsiveness in a subject or cells derived from a subject. Although, as pointed out above, some of the steroid responsive subjects were receiving steroids, their responsiveness to the steroids was not being determined or monitored. There would therefore be no motivation to combine the teachings of Yap *et al.* with the *in vitro* assays disclosed in Steel *et al.* that relate to observing the response of cells to cytokines and dexamethasone.

Likewise, Steel *et al.* does not provide a motivation to combine its teachings with those of Yap *et al.*, nor do its teachings make up for the deficiencies of Yap *et al.* Steel *et al.* describes the alterations in RNA levels of acute phase serum amyloid A (A-SAA) protein, constitutive serum amyloid A (C-SAA) protein, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in response to cytokines, monocyte conditioned medium, and/or a steroid, dexamethasone. GAPDH is considered to be a housekeeping gene that is not responsive to dexamethasone. Regarding steroid responsive genes disclosed in Steel *et al.*, Applicant submits that Steel *et al.* teaches that both A-SAA mRNA and C-SAA mRNA are only steroid responsive under certain conditions and only in certain cell lines. For example, on page 495, column 1, line 23 to column 2, line 2, Steel *et al.* states that, “[w]ith the exception of HEP3B’M’ Dex alone did not induce C-SAA mRNA significantly in any of the hepatic cell lines; however, Dex did

enhance the response to MoCM several fold in some cell lines. In Hep3B'M' cells Dex caused an increase in A-SAA mRNA levels to an equivalent level to MoCM." In addition, at page 496, column 1, lines 8-11, Steel *et al.* states that, "C-SAA mRNA was not induced significantly by MoCM and/or Dex treatment in most of the non-hepatic cells, with the exception of MRC5 cells which are induced slightly by MoCM + Dex." Thus, Applicant submits that Steel *et al.* does not provide a motivation to use either A-SAA mRNA or C-SAA mRNA as an indicia of steroid responsiveness or drug responsiveness, given the cell line to cell line variability in responsiveness to of the A-SAA and C-SAA genes to steroids. A skilled artisan would therefore not have been motivated to combine the ratios disclosed in Yap *et al.* (e.g., of a steroid responsive mRNA to a steroid non-responsive mRNA) with the assays of Steel *et al.*, as suggested by the Examiner, because Steel *et al.* did not disclose a reliable steroid responsive mRNA. In addition, Steel *et al.* would not have been motivated to look to Yap *et al.* for guidance regarding which of the steroid responsive or non-responsive mRNAs they should measure because Yap *et al.* does not disclose which of the mRNAs that they measured are steroid / drug responsive or are steroid / drug non-responsive. Thus, absent a motivation to combine the teachings of Yap *et al.* and Steel *et al.*, the references are not properly combinable under 35 U.S.C. §103(a). Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 2, 3, and 7 and the claims depending therefrom.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 22, 23, and 25 under 35 U.S.C. §103(a), contending that the claims are unpatentable over Yap *et al.*, in view of Steel *et al.* and further in view of Alkon *et al.*, U.S. Patent 6,300,085 ("Alkon *et al.*").

As discussed above, Yap *et al.* and Steel *et al.* are not combinable. Further, neither Yap *et al.* nor Steel *et al.* provides a motivation to be combined with the teachings of Alkon *et al.* or *vice versa*. Yap *et al.* discloses the use of blood samples and Steel *et al.* discloses the use of cell lines. There is no motivation to alter either of those teachings to use buccal cells as disclosed in Alkon *et al.*, as suggested by the Examiner. In addition, Alkon *et al.* provides no motivation to study steroid responsiveness. Alkon *et al.* discloses methods for diagnosing Alzheimer's disease by measuring potassium channel, intracellular calcium, and memory associated GTP binding Cp20 protein levels between Alzheimer's and normal cells. These methods are unrelated to the

Applicant's claimed methods. Thus, none of the references provides a motivation to combine their teachings, nor does Alkon *et al.* make up for the deficiencies of either Yap *et al.* or Steel *et al.*, given that the teachings of Alkon *et al.* do not relate to steroid or drug responsiveness nor measuring RNA ratios. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 22, 23, and 25 and the claims depending therefrom.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 39-40 under 35 U.S.C. §103(a), contending that the claims are unpatentable over Yap *et al.*, in view of Steel *et al.* and further in view of Chikanza *et al.* (1993) Eur. J. Clin. Invest. 23:845-850 ("Chikanza *et al.*").

As discussed above, Yap *et al.* and Steel *et al.* are not combinable. Further, neither Yap *et al.* nor Steel *et al.* provide a motivation to be combined with the teachings of Chikanza *et al.* or *vice versa*. Chikanza *et al.* discloses *in vitro* corticosteroid (CS) sensitivity tests that measure the inhibitory effect of hydrocortisone on Con-A stimulated peripheral blood MNC proliferation and also discloses the ability of CS to inhibit IL-2 and IL-4 secretion from Con-A stimulated mononuclear cells (MNC) in arthritis patients. There is no suggestion or motivation in any of the references to alter either Yap *et al.* or Steel *et al.* to examine arthritis in steroid responsive and non-responsive patients. Yap *et al.* is not concerned with measuring steroid responsiveness nor is Yap *et al.* concerned with arthritis, but rather cytokine expression in childhood nephrotic syndrome. Steel *et al.* is not concerned with arthritis, or human diseases generally, as Steel *et al.* discloses *in vitro* assays using cell lines derived from different tissues. Further, as discussed above, Steel *et al.* is not concerned with using certain genes that are known or suspected of being steroid responsive, since their A-SAA and C-SAA mRNAs are variably responsive or non-responsive to steroid. Likewise, Chikanza *et al.* provides no motivation to use ratios of steroid responsive and non-responsive mRNAs to determine steroid responsiveness. Chikanza *et al.* discloses *in vitro* corticosteroid (CS) sensitivity tests that measure the inhibitory effect of hydrocortisone on Con-A stimulated peripheral blood MNC proliferation and also discloses the ability of CS to inhibit IL-2 and IL-4 secretion from Con-A stimulated mononuclear cells (MNC) in arthritis patients. These methods are unrelated to the Applicant's claimed methods as well as the methods or purposes disclosed in Yap *et al.* and Steel *et al.* Chikanza *et al.* therefore provides no motivation to alter these teachings. Thus, none of the references provides a

motivation to combine their teachings, nor does Chikanza *et al.* make up for the deficiency of either Yap *et al.* or Steel *et al.* Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 39-40 and the claims depending therefrom.

REQUEST FOR TELEPHONIC INTERVIEW

Applicant respectfully requests a telephonic interview in order to expedite the prosecution of the claims. The Examiner is invited to telephone the undersigned at 617-310-8168 to arrange a convenient time to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

CONCLUSION

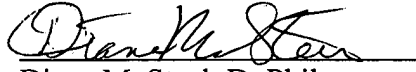
Applicant respectfully urges that all claims are in condition for allowance and requests prompt and favorable action on the instant application.

Respectfully submitted,

Date: May 10, 2004
Reg. No. 43,153

Tel. No.: (617) 310-8168
Fax No.: (617) 248-7100

3052129_1


Diana M. Steel, D. Phil.
Attorney for Applicant
Testa, Hurwitz, & Thibault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110